

71 naturally occurring *patched* receptor, wherein the amount of the *hedgehog* polypeptide is effective to promote one or more of growth, differentiation, and survival of said cells.

124. (New) A method for promoting survival of mammalian neuronal cells responsive to *hedgehog* induction, comprising treating the cells with an effective amount of a *hedgehog* polypeptide at least 80% identical to a sequence selected from SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 20, SEQ ID NO: 21 and N-terminal fragments of the preceding sequences that bind to a naturally occurring *patched* receptor, thereby increasing the survival rate of the neuronal cells.

125. (New) A method for promoting growth of mammalian neuronal stem cells, comprising treating the cells with an amount of a *hedgehog* polypeptide at least 80% identical to a sequence selected from SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 20, SEQ ID NO: 21 and N-terminal fragments of the preceding sequences that bind to a naturally occurring *patched* receptor, wherein the amount of the *hedgehog* polypeptide is effective to increase the rate of growth of the neuronal stem cells.

126. (New) The method of any one of claims 123, 124, or 125, wherein said *hedgehog* protein is administered in combination with one or more other neurotrophic factors.

127. (New) The method of claim 126, wherein said other neurotrophic factor is selected from CNTF, BDNF, and NGF.

128. (New) The method of claim 123, wherein said neuronal cells are neural progenitor cells.

129. (New) The method of claim 123, wherein said neuronal cells differentiates into cells having a selected neural phenotype.

130. (New) The method of claim 123, wherein said neuronal cells are in the central nervous system or the peripheral nervous system.

51 131. (New) The method of claim 130, wherein said *hedgehog* treatment repairs central or peripheral nerve damage.

132. (New) The method of claim 123, wherein said *hedgehog* polypeptide mimics the effect of a naturally occurring *hedgehog* protein on one or more of growth, differentiation, and survival of neuronal cells.

133. (New) The method of claim 123, wherein said *hedgehog* polypeptide comprises an amino acid sequence identical with all or a portion of an amino acid sequence designated in one of SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, and SEQ ID NO: 34.

134. (New) The method of any one of claims 123, 124, or 125, wherein said *hedgehog* polypeptide has an amino acid sequence which is encoded by a nucleic acid which hybridizes under highly stringent conditions, including a wash step of 0.2 x SSC at 65 °C, to a nucleic acid sequence selected from SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6 and SEQ ID NO: 7.

135. (New) The method of claim 123, wherein said *hedgehog* polypeptide is encoded by a nucleic acid which is at least 98% identical with all or a portion of a nucleic acid sequence designated in one of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, and SEQ ID NO: 7.

136. (New) The method of claim 123, wherein said *hedgehog* polypeptide is encoded by a nucleic acid which is at least 90% identical with all or a portion of a nucleic acid sequence designated in one of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, and SEQ ID NO: 7.

137. (New) The method of claim 123, wherein said *hedgehog* polypeptide is encoded by a nucleic acid which is at least 95% identical with all or a portion of a nucleic acid sequence designated in one of SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, and SEQ ID NO: 7.

J1 138. (New) The method of any one of claim 123, wherein said polypeptide includes a *hedgehog* amino acid sequence at least 80 percent identical with a sequence selected from residues 104-189 of SEQ ID NO: 8, residues 102-187 of SEQ ID NO: 9, residues 31-116 of SEQ ID NO: 10, residues 102-187 of SEQ ID NO: 11, or residues 101-186 of SEQ ID NO: 12.

139. (New) The method of claim 123, wherein said polypeptide includes a *hedgehog* amino acid sequence at least 90 percent identical with a sequence selected from residues 27-189 of SEQ ID NO: 8, residues 22-187 of SEQ ID NO: 9, residues 1-116 of SEQ ID NO: 10, residues 25-187 of SEQ ID NO: 11, or residues 24-186 of SEQ ID NO: 12.

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cont 140. (New) The method of claim 123, wherein said polypeptide includes a *hedgehog* amino acid sequence at least 90 percent identical with an amino acid sequence selected from residues 27-425 of SEQ ID NO: 8, residues 22-396 of SEQ ID NO: 9, residues 1-336 of SEQ ID NO: 10, residues 25-437 of SEQ ID NO: 11, residues 24-418 of SEQ ID NO: 12, or residues 24-475 of SEQ ID NO: 13, residues 1-312 of SEQ ID NO: 14.

141. (New) The method of claim 123, wherein said polypeptide includes an amino acid sequence encoded by a naturally occurring vertebrate *hedgehog* gene.

142. (New) The method of claim 141, wherein said *hedgehog* gene is a mammalian *hedgehog* gene.

143. (New) The method of claim 142, wherein said *hedgehog* gene is a human *hedgehog* gene.

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M4 144. (New) The method of claim 123, wherein said polypeptide includes an amino acid sequence which is encoded by at least a portion of a *hedgehog* gene of vertebrate origin selected from residues 64-567 of SEQ ID NO: 1, residues 64-561 of SEQ ID NO: 2, residues 1-348 of SEQ ID NO: 3, residues 73-561 of SEQ ID NO: 4, and residues 70-558 of SEQ ID NO: 5.

145. (New) The method of claim 123, wherein said amino acid sequence is represented in the general formula SEQ ID NO: 41.

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146. (New) The method of claim 123, wherein said polypeptide includes at least 150 amino acid residues of the N-terminal half of a *hedgehog* protein.

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147. (New) The method of claim 123, wherein said polypeptide binds to a naturally occurring *patched* receptor.

148. (New) The method of claim 147, wherein said *patched* receptor is a patched receptor of a vertebrate organism

149. (New) The method of claim 123, wherein said neuronal cells are selected from motor neurons, cholinergic neurons, dopaminergic neurons, serotonergic neurons and peptidergic neurons.

150. (New) The method of claim 123, wherein said *hedgehog* amino acid sequence is represented in the general formula/SEQ ID NO: 40.

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151. (New) The method of claim 123, wherein said polypeptide includes at least 50 amino acid residues of the N-terminal half of a *hedgehog* protein.

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152. (New) The method of claim 123, wherein said polypeptide includes at least 100 amino acid residues of the N-terminal half of a *hedgehog* protein.

153. (New) A method for promoting one or more of growth, differentiation, and survival of neuronal cells, comprising contacting said cells with an amount of a *hedgehog* polypeptide encodable by a nucleic acid which hybridizes under stringent conditions, including a wash step of  $0.2 \times \text{SSC}$  at  $65^\circ\text{C}$ , to a nucleic acid sequence designated in one of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, or SEQ ID No: 19, or a fragment thereof that binds to a naturally occurring *patched* receptor, effective to promote one or more of growth, differentiation, and survival of said cells.

154. (New) A method for promoting survival of mammalian neuronal cells responsive to *hedgehog* induction, comprising treating the cells with an effective amount of a *hedgehog*

21 polypeptide encodable by a nucleic acid which hybridizes under stringent conditions, including a wash step of 0.2 x SSC at 65 °C, to a nucleic acid sequence designated in one of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, or SEQ ID No: 19, or a fragment thereof that binds to a naturally occurring *patched* receptor, thereby increasing the rate of survival of the neuronal cells.

155. (New) A method for promoting growth of mammalian neuronal stem cells, comprising treating the cells with an amount of a *hedgehog* polypeptide encoded by a nucleic acid which hybridizes under stringent conditions, including a wash step of 0.2 x SSC at 65 °C, to a nucleic acid sequence designated in one of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, or SEQ ID No: 19, or a fragment thereof that binds to a naturally occurring *patched* receptor, effective to increase the rate of growth of the neuronal stem cells.

156. (New) The method of claim 125, wherein said polypeptide sequence comprises a polypeptide encoded by a nucleic acid which is at least 90% identical to all or a portion of a nucleic acid sequence designated in one of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, or SEQ ID No: 19.

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Cont 157. (New) The method of claim 125, wherein said polypeptide sequence comprises a polypeptide encoded by a nucleic acid which is at least 95% identical to all or a portion of a nucleic acid sequence designated in one of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, or SEQ ID No: 19.

158. (New) The method of claim 125, wherein said polypeptide sequence comprises a polypeptide encoded by a nucleic acid which is at least 98% identical to all or a portion of a nucleic acid sequence designated in one of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO: 8, or SEQ ID No: 19.

159. (New) The method of claim 124, wherein said polypeptide sequence comprises a polypeptide encoded by a nucleic acid which is at least 90% identical to all or a portion of a